Direct manipulation of T lymphocytes by proteins of gastrointestinal bacterial pathogens

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Direct manipulation of T lymphocytes by proteins of gastrointestinal bacterial pathogens

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Abstract

Gastrointestinal bacterial infection represents a significant threat to human health, as well as a burden on food animal production and welfare. Although there is advanced knowledge about the molecular mechanisms underlying pathogenesis, including the development of immune responses to these pathogens, gaps in knowledge persist. It is well established that gastrointestinal bacterial pathogens produce a myriad of proteins that affect the development and effectiveness of innate immune responses. However, relatively few proteins that directly affect lymphocytes responsible for humoral or cell-mediated immunity and memory have been identified. Here, we review factors produced by gastrointestinal bacterial pathogens that have direct T cell interactions and what is known about their functions and mechanisms of action. T cell interacting bacterial proteins that have been identified to date mainly target three major T cell responses: activation and expansion, chemotaxis or apoptosis. Further, the requirement for more focused studies to identify and understand additional mechanisms used by bacteria to directly affect the T cell immune response and how these may contribute to pathogenesis is highlighted. Increased knowledge in this area will help to drive development of better interventions in prevention and treatment of gastrointestinal bacterial infection.

Introduction

Gastrointestinal bacterial infection represents a significant threat to human health and welfare, with an estimated 900 million illnesses resulting in over 500 000 deaths in a single year, according to the World Health Organisation (1). Although much is known about the molecular mechanisms underlying persistence, pathogenesis and protection, significant effort is still required to devise effective intervention strategies. Bacterial immune evasion methods include expression of surface polysaccharides to resist complement-mediated killing and opsonisation, enzymes to detoxify reactive oxygen species in phagosomes, escape from phagosomes and in the case of intracellular bacterial pathogens, interference in cellular antigen-presentation and innate immune responses by proteins secreted by Type III or Type IV secretion systems (2). The role of Type III secretion in gastrointestinal bacterial pathogens is covered by many high quality reviews (eg. 3), and therefore is not the focus of this review. Relatively fewer mechanisms have been identified whereby bacteria are able to directly affect lymphocytes during infection. Further, understanding the full role of these bacterial proteins and their T cell interactions during infections, any specificity for T cells subsets, and proof that they are able to directly meet T cells in the body is crucial to establish biological importance. However, such evidence is often lacking, and a number of barriers to understanding these aspects exist.

Here, we review the known molecules and strategies that contribute to the direct subversion or dampening of the adaptive T cell response in gastrointestinal bacterial infection. In addition, we discuss the challenges and aspirations of identifying these mechanisms.

T cell distribution in the intestine

53 An understanding of the importance of T-cell targeting strategies by bacteria that
54 infect the intestine requires an understanding of the lymphoid architecture, distribution of
55 gut resident T cells, the ability of T cells to be recruited to this tissue and the nature of the
56 downstream immune response that is triggered upon infection. T cell responses in the
57 intestine are mainly governed by the gut-associated lymphoid tissue (GALT), which is similar
58 to other secondary lymphoid tissues in the body, and in mammals, consists of the
59 mesenteric lymph nodes (mLNs) and Peyer's patches (PP), the appendix and multiple
60 smaller isolated lymphoid follicles studding the intestinal wall. In addition, there are isolated
61 immune cells scattered in the lamina propria (LP) and throughout the epithelium of the
62 intestine (reviewed in 4) that contribute to intestinal immune responses (summarized in
63 Figure 1). T cell responses in the gut can be initiated from several sites. Generally in an
64 intestinal immune response, intravascular naïve T cells home to the GALT (specifically to the
65 PP and mLN), where they can meet their cognate ligand in the context of the Major
66 Histocompatibility Complex (MHC) and become activated. These T cells are then able to exit
67 the lymphoid tissue via the lymphatic vessels and enter the circulation to home back to the
68 intestinal LP (reviewed in 5) where they are able to carry out their functions. Within the
69 mucosa, dendritic cells in the LP sample antigens and migrate to the PP and mLN where they
70 are able to prime and present antigen to naïve CD4+ and CD8+ T cells, which clonally
71 expand. These T cells may become memory cells, which accumulate over time in the LP. The
72 LP is mainly enriched for the $CD4^+$ T_{reg} and T_h17 cells. In contrast, the intraepithelial
73 lymphocyte (IEL) resident T cell population is mainly composed of both T cell receptor (TCR)
74 αβ and TCR γδ (TCR αβ are generally considered "conventional T cells", TCR γδ cells are
75 often considered non-conventional atypical T cells), both mainly CD8ββ isoform. However,
76 IELs appear to lack some typical T cell surface molecules such as CD2 (adhesion molecule),

CD28 (activating co-receptor) and Thy-1 (pan T cell marker of human and mouse cells). These cells are considered "activated, yet resting" and are different compared to peripheral T cells (which express CD4 or CD8αβ isoform; reviewed in (4)).

Although there is not a large literature describing direct effects of gastrointestinal bacterial pathogens on T cells, a picture of the general strategies used to alter T lymphocyte function is emerging (summarised in Figure 2). The effects identified can be broadly assigned to three groups: those that affect T cell activation and proliferation, those that affect chemotaxis and those that cause elimination of T cells, with most of the strategies identified thus far falling into the first category. Little duplication of specific strategies across species of intestinal bacteria has been identified so far, and the mechanisms and observations described are derived from a relatively small number of bacterial species.

Proteins that affect T cell activation and proliferation

A number of bacterial proteins have been identified that act to interfere with signalling cascades in T cell activation and expansion, which are outlined below. These proteins are often soluble, diffusible factors, and can act externally to the T cell, as well as intracellularly.

Superantigens

Perhaps the earliest, well known and characterised bacterial factor with T cell-affecting activity is superantigen. Barber observed superantigen activity in *Staphylococcus* in 1914, and identified the cause to be a microorganism-derived toxin (6). Since then, there have been numerous studies characterising the activity of superantigens. One of the hallmarks of superantigens is their ability to activate a large population of T cells at very low concentrations (7, 8). At a basic level, superantigens are able to cross-link a relatively large number of T cells to antigen-presenting cells (APC) compared to normal antigen-driven activation, inducing wide spread non-antigen-specific activation of T cells, ultimately leading

to clonal deletion and anergy, thus suppressing a productive T cell response (9). Superantigens are effective because they bind outside the peptide-binding groove of MHC, they are not MHC restricted and activation does not rely on antigen internalisation and processing. In addition, they specifically require the TCR β chain, not the Vα-Vβ chain pairing required in conventional antigen recognition by the TCR (reviewed in 8).

Although most well described in *Staphylococcus*, superantigens have been identified in other bacteria, including the pathogens *Yersinia enterocolitica* (10), and *Yersinia pseudotuberculosis* (11), the latter of which most often causes a self-limiting gastrointestinal infection. However, strains of *Y. pseudotuberculosis* have also been reported to infect the gut and cause Far East Scarlet-like Fever (reviewed in 16), and many strains associated with this pathogenic infection express the superantigen *Y. pseudotuberculosis*-derived mitogen A (YPMa). Strains deficient in YPMa have been demonstrated to have decreased pathogenicity, however, growth of the bacteria was unaffected in the major immune organs after oral infection, so YPMa may have more pronounced effects in systemic infection (13), and a more recent study has linked the toxic activity of YPMa to activation of a hepatotoxic $CD4^+$ T cell subset (14).

Lymphostatin

Lymphostatin (LifA, Efa-1) is one of the largest known bacterial proteins at 365 kDa, and is a putative glycosyltransferase, expressed by enteropathogenic *Escherichia coli* (EPEC) and non-O157 enterohaemorrhagic *E. coli* (EHEC) (15). It has homology to the large clostridial toxins A and B (TcdA/B) at the N terminal portion of the protein, where the catalytic glycosyltransferase domain of TcdA/B resides (15, 16). The existence of a soluble factor capable of inhibiting mitogen-activated lymphocyte proliferation and pro-inflammatory cytokine expression was first described using crude bacterial lysates of the

prototype EPEC strain E3248/69 (17). Lymphostatin was then subsequently identified using a cosmid library screen to identify the gene responsible for this activity, which was confirmed by mutation of the *lifA* gene in EPEC (15). Recently, it was shown that lymphostatin, like its clostridial homologues, is able to bind sugar moieties, in this case UDP-N-acetyl glucosamine (UDP-GlcNAc), and has significant predicted structural homology around the putative glycosyltransferase domain. A DXD motif within this domain is necessary for UDP-GlcNAc binding and lymphostatin activity, however, formal evidence of sugar transfer and the identity of the cellular target remain elusive (16). It has been demonstrated that lymphostatin is capable of inhibiting all major T cell subsets. In addition, lymphostatin has some activity against B cells, but not natural killer cells (18). Further, the effects of lymphostatin on T cells appear to be long-lived, even in the absence of continued incubation with the protein, preventing mitogenic activation for more than 18 hours after transient exposure and withdrawal of the protein. Lymphostatin was also able to inhibit antigen-specific proliferation of bovine T cells using *Theileria parva* antigens presented on infected irradiated APCs to *T. parva* specific T cells as a model antigen system (18). These findings suggest that lymphostatin might act to permanently de-sensitise T cells to stimulus, possibly suppressing T cell responses and preventing or dampening a productive immune response and delaying clearance of infection (18). It would appear that the effects of lymphostatin interfere with signalling in a membrane proximal way, as inhibition was not achieved in T cells stimulated with Phorbol 12-myristate 13-acetate (PMA)/ionomycin, which bypass membrane signalling.

Lymphostatin is known to play an important role in intestinal colonization of calves by non-O157 EHEC strains of multiple serogroups (19, 20) and of mice by *Citrobacter rodentium* (21). However, attenuation is evident early after infection, before adaptive

responses may be expected to have developed. Alongside the ability to suppress T cell activation, lymphostatin also appears to be associated with adhesion (22), possibly as a consequence of effects on Type III secretion in some strains (19, 20). These results indicate that lymphostatin may have additional roles in infection. There are a number of unresolved questions regarding the activity of lymphostatin, including its cellular target of glycosylation. Further, in O157:H7 strains of EHEC, where full-length lymphostatin is not expressed, there is a putative homologue, ToxB, that also shows T cell inhibitory activity, as well as homology at the N-terminal end of the molecule to TcdA/B (18). This suggests that lymphostatin and lymphostatin-like molecules may be a family of proteins expressed by *E. coli* to control T cell responses to infection.

VacA

Helicobacter pylori expresses the VacA vacuolating cytotoxin, which has direct activity against T cells, specifically inhibiting T cell proliferation (23–25) as well as effects on other cells, including phagocytes and epithelial cells (likely by a different mechanism; reviewed in 23). VacA is a two domain protein, processed from a protoxin form, after secretion via a Type Va system from the bacteria (reviewed in 24). Variation in the VacA gene amongst different strains of *H. pylori* results in varying levels of toxicity among the different variants (28). Like other toxins, VacA must be taken up by the cell in order to exert its activity, and it has been shown that both domains are needed for proper uptake and function of the toxin (29). The integrin CD18, expressed on the cell surface, has been identified as being important for uptake of VacA in human T cells (30), mediated by Protein Kinase C (PKC), and activation of the T cell is required to see the active endocytosis of VacA in T cells (31). In addition, VacA is able to block calcium flux in the Jurkat T cell line (32), and

prevent IL-2 expression by blocking translocation of the transcription factor NF-AT (24, 25). Overall, the data suggest that VacA targets previously activated T cells. Using *in vivo* studies in mice, a null mutation of *vacA* was reported to impair initial colonization of mice by *H. pylori*, however, once infection by the *vacA* mutant becomes established, the bacterial load and extent of intestinal inflammation were similar to the parent strain (33). This effect is independent of an effect on T cells, as mice T cells do not express a compatible receptor that allows uptake of VacA (30).

YopH

Another example of inhibition of T cell activation by interference in T cell signalling is the YopH protein from *Yersinia*. YopH is expressed by *Yersinia spp.* that infect the gut (34), including *Y. entercolitica* and *Y. pseudotuberculosis*, and has been characterised as a protein tyrosine phosphatase (35). In *in vitro* studies, using T cell-like cell lines, YopH was able to inhibit IL-2 production induced by antigen stimulation, the effects of which were upstream of PMA/Ionomycin (36). It was apparent by Western Blotting that general tyrosine phosphorylation of signalling molecules was inhibited. YopH has also been shown to exhibit activity against B cell activation via the B cell receptor, with similar characteristics (36). These effects were independently confirmed in primary human T cells (37). In T cells, YopH is able to dephosphorylate the early signalling molecule Lck (38). Further, it has been shown that YopH interacts with a number of adaptor molecules involved in early T cell receptor signalling. Using a trapping mutant, YopH was shown to directly dephosphorylate recombinant phosphorylated Lck in an *in vitro* activity assay, while not dephosphosphorylating other associated adaptor molecules, indicating some specificity of activity (39). This is an elegant mechanism, as an effect on relatively few molecules of Lck

would have a large impact on downstream signalling due to amplification through the signalling cascade. These studies remain quite far removed from the complex *in vivo* infection, so the implications of these activities are not entirely known. However, it has been demonstrated *in vivo* that *yopH* deficient *Y. enterocolita* are drastically attenuated in oral infection of C57BL/6 mice, although colonization of the small intestine persists until at least 21 days post-infection (40). Colonization by the YopH mutant declined quickly after infection (40). Further, in an intranasal infection model, a *yopH* deficient strain was less effective at lung colonization (41). In both cases, reduced colonization was seen early in infection before one might expect an adaptive response to have properly formed, and so it remains unclear what role YopH/T cell interactions play in virulence. In addition to YopH, *Yersinia* expresses an additional protein, invasin, which may allow *Yersinia* to subvert lymphocytes, particularly T cells, to influence their motility and facilitate dissemination of *Yersinia* to distal sites (42). These two proteins may function to simultaneously neutralize T cell activation while keeping the cells intact to allow *Yersinia* infection, and redirection to other sites within the body. An invasin homologue in EPEC and *Citrobacter rodentium*, intimin (reviewed in 41), has been shown to interact with T cells, however, it is difficult to separate its direct effects on lymphocytes from the vital role it plays in gut colonization when interpreting its role *in vivo* (44, 45).

Interference with metabolic activity

T cells undergo rapid metabolic reprogramming on activation, one of the requirements of which is a source extracellular amino acids (46). Import of amino acids such as asparagine and glutamine is required to accommodate the increased metabolic load induced by aerobic glycolysis during activation and proliferation of T cells (47). There are at

221 least two examples of proteins from gastrointestinal bacterial pathogens that appear to
222 inhibit T cell activation via limiting availability of extracellular amino acids.

223 In a recent publication, Floch and colleagues (48) reported that the *Campylobacter*
224 *jejuni* protein, gamma-glutamyl transpeptidase (GGT) was capable of inhibiting mitogenic
225 proliferation of T cells *in vitro*. Although GGT is known to be important in intestinal
226 colonization by *C. jejuni* in the chicken (49), little is known about its activity on T cells.
227 However, it is tempting to extrapolate from what is known about a similar GGT that is
228 expressed by *H. pylori*. The GGT of *H. pylori* plays an essential role in colonization of the
229 gastric mucosa in mice (50). GGTs are N-terminal nucleophile hydrolases that play a role in
230 the degradation of glutathione, and GGTs across mammal and bacterial species often
231 exhibit a high protein sequence identity, with the GGT of *C. jejuni* clustering with
232 *Helicobacter spp.* (51). Treatment of mouse T cells with recombinant GGT from *H. suis*
233 inhibits CD3/CD28-stimulated proliferation in a concentration-dependent manner (52). In
234 human peripheral blood mononuclear cells, GGT also inhibits PMA/Ionomycin stimulated
235 proliferation, causing cell cycle arrest, inhibiting c-Myc and c-Raf (53). GGT more specifically
236 causes glutamine deprivation in the extracellular space of T cells, downregulating both c-
237 Myc and IRF4 which are sensitive to glutamine, and required for metabolic adaptation (54).
238 Overall, the data suggest that GGT is able to modulate the response of T cells in infection,
239 likely through control of the extracellular availability of glutamine, which is required during
240 activation.

241 A second example of a gastrointestinal bacterial protein that interferes with T cell
242 metabolism comes from *Salmonella enterica* serovar Typhimurium, which has been
243 reported to directly inhibit primary mouse T cells (55), and is thought to limit availability of
244 asparagine to T cells (56). When assessing a number of cell surface expressed molecules, no

difference was noted in levels of CD69, CD25α, CD44, and CD62L in cells infected with *S.* Typhimurium compared to uninfected controls. However, in the presence of *S.* Typhimurium, neither IL-2 nor IFN-γ were produced with CD3 cross-linking (both these cytokines are up-regulated during T cell activation). Cytokine production was restored if the cells were separated from the bacteria in a transwell arrangement, indicating that direct contact with the bacteria was required for this effect. From here, the authors extended their observations, again using *in vitro* methods with primary mouse cells, showing that *S.* Typhimurium was able to down regulate surface expression the TCR β chain, resulting in decreased gene expression, intracellular and surface protein, at least partially explaining the mechanism targeted to inhibit T cell activation (57). Not only that, but this effect was only observed in the presence of live bacteria, as treatment with heat-inactivated bacteria abrogated this effect. The effects were shown to be unrelated to Type III secretion or the bacterial virulence plasmid. It was later shown that the protein responsible for this was L-asparaginase II (STM3106; *asnB*) (58). In a mouse model of bacterial persistence, the burden of bacteria was lower in mutants lacking L-asparaginase II, suggesting that this molecule may enable bacterial persistence by dampening the T cell-mediated immune response (58). In contrast, in a screen of *S.* Typhimurium mutants in pigs, calves and chickens, a transposon insertion was not attenuating in the gut, albeit within 3-4 days after oral infection (59). Nonetheless, the characterization of the activity of the L-asparaginase II on T cells is a good example of how bacterial subversion can lead to insight into basic host cell biology. In this case these studies highlight the importance of asparagine as a nutrient in T cell metabolism and activation (60).

Interference in lymphocyte chemotaxis

The majority of T cell-interacting bacterial proteins appear to mainly exert effects on T cell activation, however, another strategy is to interfere with lymphocyte migration. For example, *Shigella* exhibit the ability to directly invade T cells and cause an inhibition in their chemokine-induced migration (61). *S. flexneri* are able to directly invade PMA-activated CD4+ T cells, but not unstimulated, unactivated, primary CD4+ cells, with substantially reduced responses to the chemoattractant CXCL12. CXCL12 signals through the chemokine receptor CXCR4, the expression of which was not perturbed in these experiments (61). The bacterial protein, IpgD, which can be secreted through the type III secretion apparatus (62), has been implicated as being responsible for this activity, by acting on the pool of intracellular phosphatidylinositol 4,5-bisphosphate (PIP2). Additionally, it would appear that IpgD is able to act intracellularly in the absence of any other bacterial effectors (61). These observations have been verified experimentally *in vivo* in mice, revealing that *S. flexneri* target CD4+ T cells in the lymph node and confirming that invasion and migration arrest occur *in vivo* (63). This discrimination between activated and non-activated T cells could result in more specific targeting of activated T cells in the lamina propria rather than the lymphoid follicles in the intestinal mucosa, thus targeting those cells that might actively respond to infection. Further, a recent publication reported the ability of *Shigella* to inject effectors into T cells in the absence of subsequent invasion, and suggest that the majority of T cells are targeted by injection only, raising the possibility that the bacteria could use a "hit and run" strategy to affect lymphocytes (64).

Elimination of T cells

A further strategy that is shared with more than one bacterial genus is seen with the induction of apoptosis in T cells by the heat labile toxins, expressed by *E. coli* and *Vibrio cholera*e, although they appear to have slightly different specificity and mode of action between families and variants of the toxin. The heat labile toxins are structurally related bacterial toxins that induce diarrhea in humans and animals (65). These toxins are oligomers consisting of an A polypeptide bound to a pentameric array of B polypeptides. The toxic effects are determined by the cell surface binding specificity of the B pentamers, and the ADP ribosylating specificity of the A subunit (66). Cholera toxin (CT) produced by *V. cholerae* binds to the ganglioside GM1 on epithelial cells via its B subunits, and when it is trafficked to the cell cytosol, it catalyzes ADP ribosylation of adenylate cyclase, leading to increased intracellular cAMP causing water secretion and diarrhea (67). However, it has additional effects on other cells, including T cells. It was demonstrated some time ago that CT was able to induce apoptosis in CD8+ T cells, although at that time the implications during infection were unclear (68). More recently, it was confirmed that CT was able to decrease the numbers of CD8 cells, and that this was not due to either a downregulation of cell surface receptors, or selective proliferation of other cell types (69). Similarly, LTIIa from *E.* coli is also able to deplete CD8+ T cells, likely by induction of apoptosis via cross-linking of the ganglioside receptors, although this has not yet been explicitly demonstrated (69). In mice injected with LT, transient induction of apoptosis mediated by glucocorticoids was seen in all thymocyte subsets, although immature T cells were more affected than mature cells (70). This effect was dependent on route of administration, and demonstrated that *in vitro* treatment of cells did not entirely reflect the *in vivo* effects observed (70). In addition, the maturation state of the T cell appears to determine the mechanism of apoptosis triggered (71). Further, although CT does not appear to invoke apoptosis in CD4+ T cells, it

does appear to be able to inhibit activation, at least based on measurement of cell surface expressed molecules (69).

There has been significant interest in using CT and LT as adjuvants in vaccination, and understanding how it is able to steer T cell responses provides insight in how to better improve vaccination, or to engineer non-toxic derivatives that are able to promote its adjuvancy (72–75).

To our knowledge, there is only one other protein from a gastrointestinal bacterial pathogen reported to have the ability to invoke apoptosis in T cells. This is the YpkA protein of *Yersinia*, which is a multidomain protein with kinase activity. Expression of YpkA from a mammalian expression vector transfected in Jurkat T cells induced significant apoptosis (76), however, its role during infection is unclear.

Concluding remarks

It is evident from the examples above that gastrointestinal bacterial pathogens have evolved diverse strategies to modulate lymphocyte function. However, the biological significance of such activity during infection remains challenging to dissect, particularly for factors that play additional roles in colonization. For such factors, the T lymphocyte response to infection by a null mutant relative to the isogenic parent will be affected by the magnitude and duration of exposure to bacterial antigens. One strategy to overcome this is to use ligated intestinal loop models and recover intraepithelial lymphocytes exposed to bacterial strains or their products *in situ* (e.g. (77)). Although, it can be challenging to stimulate such cells to proliferate *ex vivo* and loop models often hold large numbers of laboratory-cultured bacteria over the mucosa for a limited time, and thus do not simulate the normal progression of gastrointestinal infection. It is noteworthy that attenuation of

mutants lacking some lymphocyte inhibitory factors is detected before one may anticipate that adaptive responses have been generated, and further research is needed to understand their impact on early pro-inflammatory responses and lymphocyte migration *in vivo*. Further, for many of these proteins, little is known about their effects on T cells of specific subsets and differentiation states. Knowledge of which might provide further insight into their impact and timing of action during infection.

While some of the strategies outlined here rely on direct contact between the pathogen and lymphocytes (e.g. via Type III secretion), in many cases inhibition relies on diffusion of soluble proteins to meet their target cell type. Some of the factors described are active in extremely low concentrations (e.g. lymphostatin acts in the femtomolar range; (16)) and the extent to which lymphocytes in circulation are affected requires study. It is evident from the ability of Shiga toxins to cause endothelial damage in kidney glomeruli that proteins produced by gastrointestinal pathogens in the gut can act distally.

While the molecular basis of the activity of some lymphocyte inhibitory factors is well understood (e.g. VacA, YopH, IpgD), for others a need exists to identify their cellular targets and how their modification produces the observed phenotype. Such studies have the potential to yield novel insights into both the basis of pathogenesis, but also the cellular pathways and factors governing lymphocyte activation and function. With an understanding of the mode of action of inhibitory factors, it may also become feasible to design new treatments. For example, with the knowledge that *Helicobacter* may use γ-glutamyltranspeptidase to restrict lymphocyte activation via interference in glutamate metabolism, researchers have recently demonstrated that oral glutathione supplementation

can reduce gastric pathology and inflammation due to *H. suis* in gerbils (78). The extent to which this is a consequence of altered T lymphocyte function requires further study.

It is striking that relatively little direct duplication of strategies to inhibit lymphocyte function has been identified across bacterial genera. Nevertheless, the vast quantities of sequence data now generated for pathogens will facilitate the identification of homologs of lymphocyte inhibitory factors that may be relevant in other diseases and differ in mechanism. For example, a family of proteins homologous to lymphostatin occur in diverse *Chlamydia* species of veterinary and public health importance and share predicted glycosyltransferase motifs (79).

In addition to evaluating the value of lymphocyte inhibitory factors as subunit vaccines or as targets for novel inhibitors, merit exists in exploring the therapeutic potential of such molecules for disorders associated with lymphocyte proliferation or activity. A challenge of such will be ensuring specific targeting of pathology-associated lymphocytes without deleterious effects on immune function.

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FIGURES

FIGURE 1: GALT and T cell distribution in the intestine

Immune responses in the intestine are mainly controlled by gut associated lymphoid tissue (GALT), including the Peyers patches, mesenteric lymph nodes and isolated lymphoid follicles in the mucosa and lamina propria. The mucosa is also studded with intraepithelial lymphocytes. Naïve T cells can be recruited from the circulation to lymphoid organs in the intestines, where they can be activated.

FIGURE 2: Summary of T cell interacting bacterial proteins and their targets

The majority of bacterial proteins that interact with T cells are directed at modifying activation/proliferation, however, there are some proteins that affect chemotaxis and apoptosis. Where the key affected molecules are known, these are indicated, however, the details of a number of molecules remain unknown. Bacterial protein names are bounded by gray boxes. sAg= superantigen (*Staphylococcus)*, CT= cholera toxin(*Vibrio cholera*), GGT=gamma glutamyl transferase (*H. pylori, C. jejuni*), IpgD= invasion plasmid gene D (Shigella), LifA= lymphocyte inhibiting factor A (*E.* coli), LT= heat labile toxin (*E. coli)*, STM3106=asparaginase (*Salmonella*), APC= antigen presenting cell, MHC= major histocompatibility complex.

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